Reprinted from PHARMACOLOGICAL REVIEWS
Vol. 4, No. 3, September, 1952
Printed in U.S.A.

THE METHONIUM COMPOUNDS

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I. Introduction

Within the last twenty years decisive evidence has accumulated that transmission of excitation from nerve to skeletal muscle or across the ganglionic synapse is achieved by means of chemical mediation. It was from the study of the actions of drugs such as nicotine, curare and the choline esters, most of them quaternary in nature, that the chemical theory of transmission grew. At first

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the interest was chiefly in the clash with the electrical theory of transmission. But at the same time as this issue was being settled, a much better theoretical basis for the understanding of the properties of quaternary salts in general was being gained. The acceptance of the theory and the use of the techniques developed by Dale and his colleagues clarified at once the actions of well-known drugs such as eserine. Moreover it stimulated the search for new drugs with specific activities in preserving, mimicking or antagonizing the natural transmitter. It would be true to say that all discussion of drugs causing neuromuscular or ganglionic block now rests on the theory of chemical transmission, and that a large part of the experimental work on such drugs consists of a recapitulation, in one form or another, of the original experiments.

Essential to the study of such substances also were the isolation and determination of structure of *d*-tubocurarine by Harold King, the success of Bovet and his colleagues in constructing curarizing compounds synthetically, and the revival of interest in autonomic function and in ganglion blocking agents initiated by Acheson, Moe, Hoobler and Lyons. All these developments provided the background without which the recognition of the activities of the methonium salts and the analysis of these actions would have been slow and difficult. Important as this background is, however, it cannot be discussed in detail here, and the reader must be referred to the numerous reviews on the subject.

A few members of the polymethylene bistrimethyl-ammonium series, whose general formula is

$$(CH_3)_3N^+ \cdot (CH_2)_n \cdot N^+(CH_3)_3$$

were synthesised many years ago, between 1895 and 1926, as diodides or dipicrates (namely, the derivatives with n = 2, 4, 5, 6, 7 and 10; for references, see 185). The octamethylene compound, whose properties initiated our investigations, was first prepared by Harold King in recent years. A complete series of diodides, ranging from the dimethylene up to the tridecamethylene derivative, was synthesised by Zaimis in 1948 (135). At the same time, Barlow and Ing (15, 16) independently prepared the dibromides, omitting the hexamethylene member which was later described by Balaban, Levy and Wilde (9). Paton and Zaimis (135–142) confined themselves from the start to this particular series of salts, analysing in detail those compounds whose peculiarities and potency had drawn their attention. Barlow and Ing, at the same time as synthesizing the dibromides of the above series, prepared dibromides of the bistriethylammonium, bis-strychninium, bisquinolinium and bisphenyldimethylammonium series, concerning themselves particularly with the "curare-like" activity of these salts in relation to the inter-quaternary distance, rather than with the general pharmacology of the active members.

The name of "methonium" compounds for the members of the polymethylene bistrimethylammonium series has been approved by the British Pharmacopoeia Commission, and it is under this name, preceded by the appropriate numerical prefix, that they are now known.

The pharmacological studies have shown this series to contain two very

specific compounds: decamethonium, imitating acetylcholine very closely at the neuromuscular junction of certain species; and hexamethonium, specifically antagonising acetylcholine at the ganglionic synapse.

II. Physical and Chemical Properties

The methonium di-iodides are white crystalline solids, not markedly hygroscopic, very soluble in water, and form neutral solutions. The solubility of the octadecane derivative, the only higher member so far synthesized, is lower than that of the other members of the series, as would be expected. The di-iodides are stable in aqueous solutions, and can be sterilized by boiling or autoclaving. They may be boiled with acid or alkali without destruction.

The dibromides have the same properties as the di-iodides except for being both hydrated and hygroscopic. The dichlorides are still more hygroscopic than the bromides, their lower members often being difficult to dispense in the solid state (134). The uptake of moisture depends in part on the method of preparation. The bitartrate and methosulphate salts have also been prepared (8, 12).

The lower members of the methonium series have negligible surface activity; with dodecamethonium and tridecamethonium a distinct depression of the surface-tension of water is observed which becomes substantial with the octadecane derivative.

The methonium salts form insoluble salts with ammonium reineckate, and their isolation from body fluids and photoelectric determination are based on this property (185). Sparingly soluble salts of hexamethonium are formed with 2:2′ - dihydroxy - 1:1′ - dinaphthyl methane - 3:3′ - dicarboxylic acid ("embonic acid") and with its next lower homologue ("bis-oxynaphthoic acid"), and these have proved useful in the isolation of hexamethonium from mixtures (13).

All the soluble salts have been successfully given intravenously, intramuscularly, subcutaneously and orally. They are non-irritant unless given in strongly hypertonic solution (*e.g.*, 30%). The incorporation of hexamethonium in a delay-medium of polyvinyl-pyrrolidone (20%) has been used, but absorption from the site of injection is only slightly prolonged (118).

III. Estimation

Colorimetric and biological methods have been described for the detection of methonium compounds in urine, faeces and blood.

Zaimis (185) has described a photoelectric method for the determination of methonium ions, after their precipitation as reineckates. The method may be applied to urine or faeces. At least 10 mg. of methonium salt is required for an adequate estimation. The technique is therefore not sensitive enough to analyse the methonium content of the blood. The reaction used for the detection of small amounts of tetraethylammonium does not proceed for the methonium series.

For detecting low dilutions of hexamethonium, a biological method must be used. Two procedures have proved successful (129): (a) use of the antagonism

of hexamethonium to acetylcholine contracture of the frog's rectus; this permits estimations with limits of error of ±10% or better, and requires about 1 mg. of hexamethonium ion; (b) use of the blocking action of hexamethonium injected close arterially into the continuously excited superior cervical ganglion of the cat, with ganglionic transmission recorded by the contraction of the nictitating membrane. Concentrations of 0.5 μg./cc. are detectable, in a volume of 0.3– 0.5 cc.; the method is subject to the usual errors of biological assay, but estimates within 0.5 μg./cc. are readily obtained.

For detecting small amounts of decamethonium, such as appear in the urine of patients receiving the drug, the response of avian muscle can be used (187). An intravenous injection of a dose of 30 μg./kg. of decamethonium produces a retraction of the head and extension of the limbs; a typical response can be obtained with 2–3 μg. decamethonium in a chick a few days old. The test may be made with urine directly, if a volume not greater than 0.5 cc. is injected rather slowly. The contracture appears during the injection and a convenient endpoint is when the chick is again able to stand normally. The decamethonium content is determined from the duration of the contracture in comparison with that caused by standard doses of decamethonium made up (if necessary) in normal urine.

IV. Excretion

From biological tests made with urine excreted after intravenous administration of methonium compounds in man and animals, evidence was obtained that the urine possessed marked biological activity. Using hexamethonium as test substance, Zaimis (185) was able actually to isolate the unchanged compound from the urine and failed to discover any degradation product.

There is no reason to suspect, so far, that demethylation or other metabolic attack takes place in the body; so that it can be assumed, on the knowledge so far gained, that the urinary output of methonium compounds represents a measure of the amount absorbed when the drug is given by mouth, and this assumption has been fairly widely made.

After parenteral administration into man or animals, decamethonium and hexamethonium are excreted in the urine fairly rapidly, and 80–90% or more of the injected dose can be recovered (81, 120, 178, 185). The rate of excretion of decamethonium and hexamethonium is such that, in human volunteers, about 60% of the drug given has appeared in the urine 3 hours after intravenous injection, and 90% of it or more in 24 hours. An estimate of the clearance rate of hexamethonium has been made, and found to be close to that of inulin, so that the renal excretion of hexamethonium is mainly due to filtration (183).

In patients with impaired renal function, urinary excretion is slowed and the clinical effects are prolonged for as much as 24 hours after a single intravenous dose. Similarly in the nephrectomised cat under chloralose anaesthesia, the blood level of hexamethonium after an intravenous dose falls very much more slowly than in the normal animal (129). It seems clear that renal excretion is the only important route of elimination of the drug.

Absorption and Distribution

Decamethonium is poorly absorbed by mouth in animals, and roughly 50–100 times as much must be given to produce an effect comparable, at its peak, with that of a given intravenous dose (137). By the subcutaneous and intramuscular routes, about two to three times the intravenous dose is required to produce an equal degree of paralysis, although the duration of paralysis is lengthened when the former routes are used. No studies of this sort have been made in man.

Hexamethonium likewise is poorly absorbed by mouth (81, 120a). When the urinary excretion is used as an index of the amount absorbed, absorption may range from 0.2% to 34% of the dose given, usually about 5–10%. This corresponds with the clinical observation that roughly 10 times more must be given by mouth to obtain the same effects as with parenteral dosage. The part not absorbed is discharged with the faeces, and the total methonium recovered from faeces and urine after an oral dose accounts for at least 60–70% of the drug given (81, 120a). This reinforces the evidence that the drug is little or not at all metabolised in the body.

The factors controlling absorption are still obscure; but there is evidence (81) that some salts of hexamethonium are more readily absorbed from the alimentary tract than others. There is also corresponding clinical evidence that the halides differ in their relative activity by oral administration in depressing spontaneous gastric secretion (98). This is a puzzling observation since the salts when dissolved in the intestinal fluids must be completely ionized, so that the fates of hexamethonium ion and the anion accompanying it should be independent. Absorption is more complete when the drug is given on an empty stomach (81). Again this is confirmed by clinical evidence that fasting patients are more sensitive to the hypotensive action of hexamethonium (98).

After parenteral administration, the concentration of hexamethonium in the blood corresponds to a solution in a volume about 10–30% of the total body volume (121), and is probably to be regarded as passing only into the extracellular space. The view that hexamethonium cannot readily penetrate the cell membrane is concordant with its very slow entry into the cerebro-spinal fluid and into the red blood cell (129), with the manner of its renal excretion by glomerular filtration without secretion or reabsorption, and with its poor absorption from the alimentary tract. Decamethonium, like *d*-tubocurarine, fails to pass the placental barrier. Hexomethonium, however, passes fairly rapidly and, after prolonged administration, the concentration in the amniotic fluid may rise considerably above that in the maternal blood; it seems probable that the foetus secretes hexamethonium in its urine, and that there is a complete cellular barrier separating the maternal circulation from the amniotic fluid into which the urine passes (180–182).

The extracellular existence of hexamethonium follows from its quaternary nature. It is generally accepted that, compared with free bases, ions penetrate cell walls very slowly. Salts of quaternary nitrogen in aqueous solution can only exist in the ionized form, so that such slowness of permeation into cellular ele-

ments of the body is to be expected. It is further likely that other ganglion blockers will be of the same character, since they must be similar to acetylcholine (itself a quaternary salt) in order to be able to compete with it satisfactorily. It is probable therefore that most ganglion blockers will be poorly absorbed by mouth, will dissolve in the extracelullar fluid and will be excreted at a rate comparable with that of inulin. The major difficulty about absorption in clinical practice is not so much that it is slow as that it is unpredictable. If ways were found to render absorption more constant, this would do much to overcome the difficulties of oral administration.

V. Neuromuscular Action of Methonium Salts

Decamethonium first received attention as being the most active member of the series in causing neuromuscular block. In its main features this action is superficially like that of drugs such as *d*-tubocurarine, and it satisfies the traditional criteria for curare-like action first laid down by Claude Bernard. In an animal in which sufficient decamethonium has been given to abolish the response of the muscle to excitation of its motor nerve, nervous conduction remains normal, and the muscle can still be excited directly by electrical stimulation. The further criterion, imposed by the theory of chemical transmission, that acetylcholine release should continue during paralysis by decamethonium, is also satisfied. It is this property of neuromuscular block in which the practical usefulness of the drug has been found, and it has proved a competent substitute for *d*-tubocurarine in clinical practice, offering the advantages of high activity, freedom from histamine-releasing and ganglion-paralysing activity, and easy synthesis without need for biological standardization. The statement sometimes made, therefore, that decamethonium is a "curare-like" drug is true in so far as it does indeed produce a true neuromuscular block, and, in clinical practice, useful muscular relaxation.

It has turned out, however, from the earliest experiments that there are numerous and fundamental differences between the actions of decamethonium and those of *d*-tubocurarine and similar drugs (38, 137, 27). The recognition and analysis of these differences has helped to clear up some of the anomalies in the pharmacology of the neuromuscular junction, so that detailed discussion of these differences is necessary, which will lead to a comparison of the modes of action of the two drugs.

1. Modes of neuromuscular block

By neuromuscular block was meant originally, as we have just seen, a motor paralysis which did not involve loss of excitability of nerve or muscle. With the advent of the theory of chemical transmission, offering for the first time a rational basis for the action of curare, the further criterion, that the drug producing neuromuscular block should not prevent the release of acetylcholine, represented a still more delicate test that the drug concerned was not affecting nervous structures. At this time the production of neuromuscular block was usually typified by the action of drugs like curare and much evidence accumu-

lated that they exerted their effects by antagonizing the action of acetylcholine at the motor endplate, as was originally postulated by Dale, Feldberg and Vogt (41).

In recent years the chemical theory of neuromuscular transmission has been elaborated and has become generally accepted. The usual picture of the transmission process is as follows: a nerve impulse traverses the nerve terminations, causing the release of acetylcholine on to the closely adjacent motor endplate. The motor endplate becomes depolarized to a degree sufficient to excite (by electrical spread) the adjacent muscle membrane and so initiates a propagated action potential with accompanying muscular contraction. The release of acetylcholine is very rapid, and its destruction, by cholinesterase concentrated at the endplate region, is also rapid so that the depolarization of the endplate, recognized electrically as the "endplate potential", is a very transient phenomenon, complete in a few milliseconds. After this interval the junction is ready to transmit another impulse. In normal transmission, therefore, the released acetylcholine produces an endplate potential which, as soon as it has reached a certain threshold value, is swallowed up in the much larger propagated muscle action potential. In the curarized muscle the endplate potential is progressively reduced to below this threshold value, until propagation ceases and the muscle contraction is abolished; the further action of curare can only now be recognized experimentally in the continuous gradual depression of the endplate potential.

This view of neuromuscular transmission is also essential to the understanding of a second mode of neuromuscular block, which (in anticipation of our later discussion) we shall refer to as block by depolarization and shall contrast in detail with block by competition. In such block, produced for instance by decamethonium in the cat, the pharmacological lesion of the transmission process is not that of diminution of transmitter action but of exaggeration of such action, for drugs producing block of this kind act by virtue of an ability to produce a persistent depolarization of the endplate, from which follows an electrical inexcitability of the endplate region sufficient to prevent endplate potentials otherwise adequate to their task from successfully exciting the adjacent muscle membrane. Although the ultimate defect in transmission blocked in this way is an electrical one, this implies no qualification of the chemical theory of transmission, for it is the specific chemical sensitivity of the endplate region which enables the prolonged depolarization produced by these agents to occur. In fact the existence of this mode of block emphasises the significance (already pointed out in the early papers) of the presence of cholinesterase close to the point of acetylcholine action, in such a way as to prevent persistent depolarization occurring naturally and inducing block during normal activity.

2. Characteristics of competitive neuromuscular block

There are a number of characteristic features of block by substances raising the endplate threshold to acetylcholine. A large number of substances of this sort, naturally occurring or synthesized, are known, but there is no doubt that *d*-tubocurarine must be chosen as the representative of this group since it is by

far the most thoroughly studied. (It must be remembered, however, that there are indications (114, 131) that a small part of its activity is due to properties other than that of competition with acetylcholine, and the ideal representative has probably yet to be found.)

1.) The action of *d*-tubocurarine at the neuromuscular junction is simply that of pure competition; this results in a single uniform picture of neuromuscular paralysis. The course of the paralysis is similar in all species and with all muscles and is never preceded by potentiation of the twitch nor accompanied by contracture. The scattered exceptions to this statement [evidence of contracture of the dog's denervated gastrocnemius (114) and of denervated rats triceps (95)], do not significantly alter this generalization.

2.) The muscle partially paralysed by *d*-tubocurarine cannot maintain a tetanus at its initial strength. Although, in a lightly curarized muscle, the tension may initially be comparable to that of a normal muscle, it falls rapidly thereafter to a much lower level. As the dose of curare increases and as the frequency of tetanisation increases, the ratio of the subsequent contraction height to the initial tension becomes smaller and smaller, and finally becomes zero even though there may still be a fairly vigorous initial twitch. The cause of this flagging tetanic contraction is not established, although no doubt a waning of the acetylcholine output per nerve volley as the tetanus proceeds is an important factor. It constitutes, however, an important aspect of the action of curare-like substances and contributes, for instance, to the greater depression of tetanic activities (such as respiration) than of muscle twitches (141).

3.) Muscles vary appreciably in their sensitivity to *d*-tubocurarine. It has long been known that ocular, cranial and bulbar muscles and those of the hand are outstandingly sensitive. In the cat, likewise, soleus is much more sensitive than tibialis, and the respiratory muscles resemble soleus (141).

4.) Block by curare is antagonized by a wide range of drugs and procedures, including anticholinesterases, adrenaline, asphyxia, potassium, previous tetanisation, acetylcholine and other depolarizing drugs, phenol, and the *m*-OH phenylalkylammonium compounds (for references, see 94, 126, 128).

5.) Block by curare is intensified by substances which raise the endplate threshold to acetylcholine, such as ether anaesthesia, atropine (in large doses) and other substances producing neuromuscular block in the same way as *d*-tubocurarine (137, 141, 143).

6.) The presence of curare diminishes the effect of depolarizing drugs, if administered beforehand, and reverses it if given subsequently (38, 112, 137).

7.) If cathodal current is passed at the endplate region of a partially curarized muscle, the intensity of the block is instantly diminished and normal transmission may be restored. Anodal current, on the other hand, intensifies the paralysis (*cf.* 31a).

3. Characteristics of neuromuscular block due to endplate depolarization

We have taken decamethonium in its action on cat, avian and frog muscle as the best representative of drugs producing depolarization block, and in de-

scribing its effects on these muscles we shall be illustrating the diverse appearances of the same basic process.

Neuromuscular block by depolarization of the endplate presents a complex picture, for there is always detectable a sequence of neuromuscular excitation followed by depression of transmission. The manifestations of this sequence vary with different muscle preparations and with different species so that the same process may give rise to a situation in which either repetitive firing, or contracture or block of transmission predominates.

a) *Cat muscle.* The paralysing action of decamethonium in the cat is usually heralded by a brief period of fasciculation of the muscle and potentiation of the single twitches. With small doses, such fasciculations may be all that is seen. If the drug is injected close intra-arterially into the tibialis, a twitch of the muscle may be produced by small doses, 3–5 times more than is required for a similar action by acetylcholine. All these reactions are due to repetitive discharge from the neuromuscular junction either spontaneously or in response to single shocks (137). The electrical changes accompanying this are discussed later, together with the changes accompanying complete block.

An analysis of these stimulant effects by Zaimis (186) established that they cannot be attributed (as had been postulated previously) to the weak antiesterase action of decamethonium, and emphasized the analogies between decamethonium and acetylcholine. The evidence against an action through anticholinesterase activity was (1) that the stimulant action was still demonstrable in the presence of a known anticholinesterase in concentration sufficient to inactivate all the enzyme; (2) that the stimulant action did not parallel the antiesterase action when these were compared in a series of compounds, including tetramethylammonium; (3) that the stimulant effects were transient and different from those elicited by anticholinesterases in many respects. This conclusion receives corroboration from the fact that the powerful antiesterase, TEPP, in doses much greater than necessary for complete cholinesterase activation, fails to produce a twitch of the cat's tibialis when injected close intra-arterially (50).

Further evidence that the potentiation of the twitch and the spontaneous fasciculations are not at all due to the weak antiesterase activity but to the active acetylcholine-like action of decamethonium was obtained from denervated cat muscle. In small doses decamethonium produces a twitch if given close intra-arterially, the contraction being associated with propagated action potentials, and in larger doses causes typical contractures during which no more rapid action potentials can be detected. These effects are qualitatively identical with those produced by acetylcholine, but cannot be produced by anticholinesterases (186).

Depolarization of the Motor Endplate (30, 31a). The endplate depolarization by decamethonium, as by any other depolarizing drug or by electrical stimulation, is initially associated with excitation or increased excitability. It is during this phase that spontaneous fasciculation and potentiation of the twitch with repetitive firing to single nerve shocks are seen. But as the depolarization persists, the phase of increased excitability passes over into inexcitability. The succession

of cathodal excitation by cathodal block as cathodal current continues to flow is, of course, familiar in peripheral nerve. It may be readily reproduced by the application of a cathode to an endplate region of a normal, or better still, a partially curarized, muscle. The sequence of endplate facilitation and endplate inexcitability then reveals itself by a period of enhanced transmission followed by onset or intensification of neuromuscular block.

During neuromuscular block by decamethonium, as well as during its stimulant action, it is only the endplate region and its immediate environs that is depolarized, and even after the largest doses and with the lapse of hours, the membrane potential of muscle fibre away from the endplate region remains unaltered. The area of depolarization in the endplate region spreads slightly with time to involve the immediately adjacent muscle membrane, and it is during this process that electrical inexcitability develops. This inexcitability, greatest at the point of maximum depolarization, can be revealed in three ways: by a raised threshold to artificial electrical stimulation; by the block, at the endplate region, of the passage of a muscle action potential along the muscle; and by the raised propagation threshold at which an endplate potential will just set up a muscle action potential. In consequence of this depolarization and electrical inexcitability, the endplate potential is set up in the middle of an area of inexcitable membrane, and further, the potential itself is diminished in so far as the membrane is already partly depolarized. From these causes results the neuromuscular blocking action. The block does not bear a constant relation to the depolarization, but it is deeper the longer the depolarization has lasted; this is probably because, as just mentioned, the depolarization spreads slightly with lapse of time by discharging the adjacent membrane so that an everwidening area of inexcitable tissue comes to separate the endplate potential from the nearest normally excitable area of muscle.

None of these electrical changes takes place with *d*-tubocurarine, but they can be reproduced with acetylcholine, or by tetanization in the presence of anticholinesterases. The action of decamethonium thus can be regarded as being in principle exactly the same as that of acetylcholine, save for being spread out over a much longer period of time.

The effects produced by decamethonium in the cat appear to be due solely to this endplate depolarization, and are not accompanied by competition with acetylcholine at the endplate. This is shown not only by the evidence already described, but also by further experiments in which anodal or cathodal currents are passed at the endplate regions for brief periods. In the normal and in the curarized muscle, the application of an anode, which hyperpolarizes the membrane, will cause or deepen neuromuscular block, whereas a cathodal depolarization will lessen it (provided it is not maintained for so long as to produce a cathodal block). But in the muscle paralysed with decamethonium, a cathodal current now immediately deepens the paralysis, and it is with an anode, which removes the depolarization, that the block can also be removed. Were the block due to any curarelike action, such a result could not be obtained. The block by decamethonium therefore is strictly attributable to the depolarization, vary-

ing in intensity with the degree and extent of the latter, and passing off as the depolarization passes off or is removed.

Neuromuscular block in the cat due to decamethonium has the following further characteristics (46, 101, 128, 137, 141).

1. Under the influence of decamethonium, the tension of a tetanus is well maintained for the duration of the tetanus.
2. Muscles differ in sensitivity to decamethonium as they do to *d*-tubocurarine, but in the opposite direction. Thus tibialis is particularly sensitive in the cat, whereas soleus and the respiratory muscles are resistant.
3. Block by decamethonium in the cat is not easily antagonized. Anticholinesterases, potassium, asphyxia and previous tetanization are ineffective. Adrenaline has diverse effects according to the route of administration.
4. Substances raising the endplate threshold to acetylcholine (such as penta- or or hexamethonium, *d*-tubocurarine, tetraethylammonium, and ether anaesthesia) diminish the activity of decamethonium.

Studies on rat-muscle have also led to the conclusion that decamethonium in this species exerts an "acetylcholine-like" depolarization of the endplate. Some differences in detail from cat muscle remain to be analysed (95, 96).

(b) *Avian muscle* (33, 187). In adult fowls or in chicks an intravenous injection of decamethonium causes a rigid extension of the limbs and retraction of the head. This is a peripheral effect and the shortening of the muscle is a true contracture. If the dose is lethal the animal dies in contracture; if the dose is below the lethal level the recovery when it occurs consists of an abrupt return to normal.

If decamethonium is injected during the recording of maximal motor nerve twitches of a normal gastrocnemius it produces a double mechanical response consisting of a quick initial contraction followed by a prolonged contracture. Electrical recording shows that the quick response is accompanied by an outburst of action potentials which are cut short by the onset of the slow contracture.

Avian muscle gives an identical response to acetylcholine. *d*-Tubocurarine, on the other hand, causes the usual flaccid paralysis in birds, the block being antagonized by anticholinesterases and by tetanus, and (as in mammals) actually antagonizes the action both of acetylcholine and of decamethonium.

(c) *Frog muscle* (137). Decamethonium produces a contracture of the frog's rectus abdominis, which sums with that produced by acetylcholine, and is antagonized by *d*-tubocurarine, hexa- and pentamethonium, and atropine in large doses. It still produces this contracture when all the cholinesterase in the muscle is inactivated. The contracture is relaxed by anodal current and enhanced by cathodal current (60).

4. Relation of mode of action to differences between decamethonium and d-tubocurarine

An attempt has been made elsewhere to relate the differences in the picture of neuromuscular block due to decamethonium from that due to *d*-tubocurarine

to their respective actions (128). This argument will not be repeated here, but may be summarized as follows: (1) the presence or absence of stimulant actions and the ability or otherwise to produce contracture correspond precisely to the presence or absence of endplate depolarization; (2) the inverse relationship between the sensitivities of a muscle or a species to the two drugs and their mutual symmetrical antagonism follows from their diametrically opposed modes of action; (3) the lability of the block by *d*-tubocurarine is because the magnitude of the endplate local response to released acetylcholine is reduced to levels at which small changes in this local response produce big changes in transmission, whereas the stability of block by decamethonium arises from the fact that the local response is close to maximal and the block is due to inexcitability of the membrane to the endplate region.

The following summary of the differences between the two drugs has been compiled to indicate those which are most useful in identifying the type of action of a given substance, and to bring out the contrasts between the two pharmacological pictures.

	Actions of depolarizing substance resembling decamethonium	*Actions of competitive blocking substance resembling d-tubocurarine*
A. *Cat Muscle*		
1) Mutual interactions	Potentiates and is potentiated by decamethonium Antagonizes and is antagonized by *d*-tubocurarine	Antagonizes and is antagonized by decamethonium Potentiates and is potentiated by *d*-tubocurarine
2) Inverse relationship on different muscles	Cat tibialis more affected than soleus and respiration	Cat soleus and respiration more affected than tibialis
3) Stimulant actions in normal muscle	Potentiation of twitch with repetitive discharge Spontaneous fasciculations	No stimulant action
4) Denervated muscle	Contracture	Antagonism of the contracture produced by a depolarizing drug
5) Stability of block	Stable	Block increased during a tetanus, diminished after it; antagonism by adrenaline, potassium, anticholinesterases, depolarizing substances, asphyxia, phenol
6) Electrical characteristics	Endplate depolarization with inexcitability of endplate region; block intensified by cathode, relieved by anode	No electrical change at endplate, and normal excitability; block intensified by anode, relieved by cathode of short duration
Avian Muscle	Contracture of limb and neck muscles	Flaccid paralysis and antagonism to contracture
Frog Muscle	Contracture	Antagonism to contracture produced by depolarizing agents

In summary, the two forms of neuromuscular block, when seen in pure form in cat, man, bird and frog, may be contrasted in various ways, expressing the

same phenomena in different idioms. Block by *d*-tubocurarine-like substances is mediated by competition with acetylcholine, leading to a depression of transmitter action, of contracture, of cathodal excitation, and of excitatory state at the endplate. Block by decamethonium-like substances, on the other hand, is due to an acetylcholine-like action, to abnormally prolonged transmitter-like action, to endplate contracture, to cathodal block, or to persistent endplate depolarization.

5. Neuromuscular block of intermediate character

The work on cat, human, avian and frog muscle accounts for the action of decamethonium as being purely that of the production of a persisting depolarization, which can be contrasted with the purely competitive action of *d*-tubocurarine. But work on certain other species shows that decamethonium can cause in these species a neuromuscular block which differs in many ways from the block accompanying pure depolarization in the cat (187). Thus in the monkey there is no initial potentiation of the twitch, the tetanus is poorly sustained, and the block is antagonised both by anticholinesterases and following the tetanus. Further, if one records simultaneously from the tibialis and soleus, a transition from one type of action to the other is seen; thus at first tibialis is most affected and soleus less (just as with decamethonium in the cat), but as doses are repeated the tibialis becomes less sensitive and the soleus more so, until it may be possible to obtain complete block of soleus, with tibialis still unparalysed, just as can be done in the cat with *d*-tubocurarine. This transition may be so rapid with tibialis that the muscle may fail to be paralysed at all by the second injection of a dose which at first produced almost complete paralysis. In order then to produce the same degree of paralysis it is necessary to give four or more times the original dose.

The impression gained from such experiments, which might be thought to provide a typical example of "tachyphylaxis", is that the phenomena seen in the monkey are like those obtained in the cat when an injection of *d*-tubocurarine is interposed between doses of decamethonium. Similar results have been obtained in dogs, hares, guinea-pigs and rats. Thus the muscles of different species may have widely divergent properties, and the mode of action of a quaternary molecule is determined not only by its own structure but also by the properties of the muscle concerned. The analogy between this "tachyphylaxis" and the effect of interposing *d*-tubocurarine suggests that decamethonium may have a dual mode of action in these species. For instance, it is possible that while the molecules of decamethonium at first adhere in the specific way necessary to produce depolarization of the endplate, their grip subsequently changes so that from a depolarizing substance decamethonium becomes a competitive inhibitor.

A similar transition from the picture of depolarization block to that of competitive block can be seen, with higher members of the methonium series, in the cat and with avian muscle. Thus, after an injection of tridecamethonium into the chick, contracture follows immediately on the injection, but slowly there ensues a stage where the legs are contracted but the head is paralysed, until finally there appears a typical flaccid paralysis. Similarly, in the cat, successive injec-

tions of tridecamethonium lead to an increasing refractoriness to paralysis of tibialis and an increasing relative effect on soleus.

6. Variation of potency of decamethonium with species

One of the outstanding problems raised by decamethonium was the varying sensitivity of different species, in contrast with their relatively uniform reaction to *d*-tubocurarine. The observations just described provide a partial explanation. In species where depolarization is the only mode of action of decamethonium (cats, birds), sensitivity is great. It is only when a competitive blocking element appears that the muscle becomes more resistant to decamethonium. It may readily be assumed that under such circumstances decamethonium is interfering with its own depolarizing blocking action. Such a view places the problem of the species difference in a very different perspective, and the question becomes that of why the muscle of different species should change the character of the action of decamethonium, rather than why decamethonium should have a greater affinity for one endplate region than another.

7. Actions of decamethonium in man

Decamethonium has proved a satisfactory relaxant in clinical use, for surgical operations (7, 8, 19, 52, 53, 82, 83, 88, 92, 123, 125, 156, 164, 166, 174, 175, 180), for abating the force of therapeutic convulsions (43, 44, 76, 87, 117), and in the treatment of tetanus (100); the clinical reports cited may be consulted for many details about the actions in man. Responses to decamethonium are not not influenced by age or sex (117). It is generally agreed that decamethonium has a shorter duration of action than *d*-tubocurarine, making it suitable for short-lasting operations, and that when recovery from its effects begins it takes place rapidly without postoperative complications. It gives no signs of histamine-release, and patients in whom *d*-tubocurarine produced bronchospasm have received decamethonium without incident (44, 117). Neostigmine has no antagonistic action to decamethonium in man (76). The suggested use of penta- or hexamethonium as an antidote has not proved successful because the ganglion blocking action of these drugs leads to substantial falls of blood pressure in some subjects but the relatively short action of decamethonium diminishes the need for any antidote. The sparing of respiration which is so prominent in the cat is less noticeable in man, although no quantitative studies have yet been made on anaesthetised subjects. Unna and his colleagues found, in conscious volunteers, that decamethonium affects the respiration more in proportion to its depression of the strength of the hand-grip than does *d*-tubocurarine or its dimethyl ether (171). Davies and Lewis, however, in clinical practice of convulsion therapy, found the respiration less affected by decamethonium, for a given relaxation of the convulsion, than by *d*-tubocurarine (43, 44). The intractable problems of assessing such drugs in clinical practice are discussed by Paton and Zaimis (140), by Unna et al. (172) and by Unna and Pelikan (173). Decamethonium has been used in a wide variety of operations, but some difference of opinion exists as to the operations for which it is most suited; thus some find it inferior to *d*-tubocurarine for intubation (74), whereas others prefer decamethonium to other

relaxants (7, 175). It seems probable that these differences correspond to variations in personal techniques and in previous experience with these relaxant drugs. Decamethonium has proved as unsuccessful as other muscle relaxant drugs in the treatment of spasticity (77).

The question arises whether human muscle in its response to decamethonium corresponds more closely to the cat or the monkey. Stimulant effects often precede the paralysis in unanaesthetized subjects (124, 171, 39), and it has been shown by electromyography that these effects are accompanied by a discharge of fibrillary action potentials as well as by motor unit discharges. (39). The ineffectiveness of anticholinesterases against the paralysis produced by decamethonium, the antagonism of a previous dose of *d*-tubocurarine to decamethonium, the capacity of the partially paralysed muscle to sustain a tetanus, and the failure of the tetanic activity of convulsion therapy to accelerate recovery from decamethonium paralysis (156) all correspond to an action by depolarization of the endplate. Pelikan *et al.* have described "tachyphylaxis" to decamethonium in conscious volunteers (143), but this has not been reported clinically (*cf.* 18); indeed Keir has successfully treated a case of tetanus by repeated doses of 2–4 mg. decamethonium every 3–4 hours, giving a total of 135 mg. (100). Finally, the activity of decamethonium in man corresponds closely to that in the cat, at 30–40 μg/kg. It is clear therefore that decamethonium is a depolarizing drug in man, and that whatever may be the evolutionary relationship, human muscle is closer pharmacologically to cat muscle than to that of the monkey.

Two further results of some importance have been obtained from studies by Churchill-Davidson and Richardson of the action of decamethonium on human volunteers (39). First the effect of decamethonium on a muscle varies inversely with the blood flow through it. Thus, in an arm in which sympathetic tone had been released by sympathetic block, it proved impossible to paralyse the abductor digiti minimi by injection of decamethonium into the brachial artery, although sufficient of the drug was given to produce general systemic effects. On the other hand, after an intravenous injection, a chilled limb was more deeply and longer paralysed than a control limb. These results may be important in interpreting some of the details of the action of decamethonium.

Secondly, the same authors have extended the observation by Sellick (157) that the myasthenic patient is not abnormally sensitive to decamethonium, and have further shown that some patients are actually greatly resistant to its action. This represents an important fact about myasthenia, and implies that the threshold of the myasthenic endplate is raised to depolarizing agents. Those theories which attribute the disorder to deficiency in acetylcholine release, or to its abnormally rapid destruction, receive no support from the response of the myasthenic muscle to decamethonium.

8. Relation to other neuromuscular blocking agents

We have interpreted the action of the methonium salts as being that of pure depolarization, pure competition, or a mixture of these two; other drugs active at the neuromuscular junction can be classified in a similar way. Among those

for which there is good evidence that they are fairly pure depolarizing agents may be included succinylcholine and adipylcholine (23, 33, 133, 176a, and 22, 67–71). A larger number must be regarded as competitive blocking agents, such as the dimethylether of *d*-tubocurarine and the synthetic compounds structurally similar to it (165), the toxiferines (103, 131) and related natural alkaloids, and flaxedil (21). Just as with *d*-tubocurarine, there is evidence that flaxedil may, under special circumstances, have a feeble stimulant action (28, 151a), but its general behaviour and its interactions with depolarizing drugs are typical of competitive block.

Several compounds with a double action comparable to that of tridecamethonium in the cat or decamethonium in the monkey have also been described; for instance, in the alkyltrimethylammonium series studied by Dallamagne and Phillipot (42, 145), it appears that the lower members have chiefly acetylcholine-like properties, depolarizing the endplate (129), whereas the higher members have a double mode of action. Similar results have been obtained with a series of choline esters of adipic acid (67–71), in which methyl groups on the choline nitrogen atoms were successively replaced by ethyl groups. Adipylcholine itself seems to be purely depolarizing, and this is still true when one ethyl substitution is made. With three ethyl substituents on each nitrogen atom it becomes curare-like and antagonistic to the parent compound. But the diethylmethyl derivative is intermediate in its properties, so that it can, for instance, both produce a contracture of avian muscles and also terminate a contracture if it is elicited by the parent substance.

An understanding of the modes of action of these compounds throws considerable light on some of the puzzling interactions between drugs active at the neuromuscular junction. A typical example of such interaction exists in the experiments by Grace Briscoe (25) who found that although neostigmine will relieve block by curare, neostigmine can also produce block itself in the muscle tetanised at a fairly high rate, and that curare, so far from accentuating this block, can actually partially restore normal transmission; she was faced with a situation in which two drugs were capable, under some conditions, of lessening neuromuscular block, and under other conditions of causing or increasing it. But a precisely analogous mutual antagonism between other depolarizing and competitive drugs is now known to exist, and her results are obviously to be interpreted as the consequence of the interaction of the competitive blocking action of *d*-tubocurarine with the depolarization produced in the presence of neostigmine partly by its own direct action, partly by the preservation of acetylcholine released during a tetanus.

VI. Ganglion-Blocking Actions of Methonium Salts

As the length of chain between the quaternary nitrogen atoms is shortened, the neuromuscular action of these salts diminishes very rapidly between the nonane and heptane derivative, to become almost negligible for hexamethonium. Large doses of hexamethonium, can indeed, produce head-drop in rabbits, and, potentiate *d*-tubocurarine. Such vestigial neuromuscular action as it possesses

is competitive in nature since it does not depolarize the endplate region and since it antagonizes the action of depolarizing substances such as acetylcholine decamethonium and succinylcholine, as well as the effect of anticholinesterases (49). But a new action now appears, that of paralysing transmission across the ganglionic synapse. This property is at its greatest in the pentane and hexane derivatives, and it is these compounds that have been most closely studied.

1. Site and mode of action

The proof that penta- and hexamethonium specifically paralyse the transmission at the ganglionic synapse has been obtained chiefly with the cat's superior cervical ganglion (142). After administration of a dose sufficient to abolish completely the contraction of the nictitating membrane to preganglionic stimulation, postganglionic stimulation is still fully effective, and the nictitating membrane responds normally to injected adrenaline. Further, hexamethonium in very large doses injected into the arterial inflow of the perfused ganglion fails to reduce acetylcholine output from the preganglionic nerve terminations when the preganglionic trunk is stimulated. These results show that hexamethonium and pentamethonium must act at the synapse itself, rather than on any postganglionic or preganglionic structure. The same conclusion follows from such observations as that hexamethonium will abolish the depression of blood pressure and bradycardia produced by vagal stimulation without affecting that produced by acetylcholine; that it will lower the blood pressure without lessening the pressor response to adrenaline; that it will paralyse salivary secretion to chorda stimulation without reducing that to carbamylcholine, (178), that it will reduce the gastric secretion to stimulation of the vagus nerve, but not to histamine or test-meals (178), and that it will reduce the rapid spontaneous contraction and peristaltic activity of the guinea pig ileum but not the effects of acetylcholine or histamine (57).

The mode of action is that of simple competition. A small dose of hexamethonium antagonises the excitant action of acetylcholine, nicotine, or tetramethylammonium on the blood pressure or superior cervical ganglion; the stimulant action reappears if large doses of those drugs are given but can again be removed by increasing the dose of hexamethonium. There is never any trace of stimulant effects by penta- or hexamethonium even with large amounts injected arterially into the ganglion. No depolarization of the ganglion can be detected if sought for by electrical recording of the potential between the ganglion body and the postganglionic trunk during the action of the drug (130, 132).

Methonium salts are therefore pure competitive blocking agents at the ganglionic synapse. Although highly active in competing with acetylcholine at this site, they lack the other properties which often accompany a relationship to acetylcholine; thus they have trivial neuromuscular blocking action, no atropine-like action, no atropine-sensitive muscarine-like action, and they do not inhibit cholinesterases. Compared with the two other important pure inhibitory ganglionic blocking drugs, *d*-tubocurarine and tetraethylammonium, they are more specific. Thus they lack the histamine-releasing power which complicates the

vascular effects of *d*-tubocurarine, and do not produce paraesthesiae, repetitive discharge of nerve, or secretion of adrenaline-like substances from the liver and adrenal glands as does tetraethylammonium. They furnish therefore, drugs of remarkable specificity and are consequently of great use in any analysis in which ganglionic activity may be concerned. Hexamethonium has in fact already proved a useful tool in analysing the action of various drugs on the intestine, in studying the action of ganglionic stimulants and in investigating the question of intestinal adrenergic ganglia (1, 2, 4, 57).

2. Cardiovascular actions

The injection of hexamethonium into the anaesthetized cat causes a fall in blood pressure of fairly gradual onset, depending in size on the initial blood pressure level. With low blood pressures due (for instance) to destruction of the spinal cord, hexamethonium has no depressor effect, even in large doses, from which it may be inferred that it possesses no cardiac depressor action or peripheral vascular action of its own. In the perfused cat's heart, no change in coronary blood flow could be obtained except with very large doses which caused an increase in force of the beat and a rise in flow preceded by a small fall. In the dog's heart, only small and transitory actions on flow were seen, never in the direction of diminution. In the perfused limb, a slight vasodilatation with big doses has been recorded (178). In the rabbit, striking vasodilatation of the ear occurs, which can lead to a 10 to 20-fold increase in heat output from the ear.

Besides the reduction of sympathetic tone produced by penta- or hexamethonium, reflex autonomic activity is modified. In the unanaesthetized dog, in which respiratory arrhythmia of the heartbeat is usually marked, the injection of hexamethonium abolishes the arrhythmia. In cats, the rise in blood pressure due to asphyxia is reduced, presumably in part by paralysis of sympathetic vasomotor action, in part by reduction of the pressor response to splanchnic nerve stimulation (57a). The pressor action of sympathomimetic amines is increased and prolonged after hexamethonium, presumably because the reflex compensatory mechanisms have been inactivated.

3. Gastrointestinal effects

The effects on the motility of the viscera vary with the species (142, 178). In the cat, an injection of hexamethonium leads to increased frequency and strength of contractions, and to spontaneous activity, of the stomach and small intestine. In the rabbit, however, there is a reduction of gastric mobility, and the rabbit's small intestine forms an excellent test object for showing the abolition of the peristaltic reflex by ganglion-blocking methonium salts. These variations probably correspond to the varying preponderance of sympathetic and parasympathetic activity in the two species. Gastric secretion, elicited in the dog by repeated stimulation of the vagus nerve, is also depressed in volume and in acid and pepsin content. The pepsin content is the last to return to normal as the action of the drug passes off.

Salivary secretion, to stimulation of the chorda tympani in the cat, is abolished

by relatively small doses of hexamethonium although the response to carbamylcholine is little altered (178).

On the isolated intestine hexamethonium has no effect on the contractions produced by histamine or pilocarpine, and possibly a very slight effect on the contraction to acetylcholine. It reduces or abolishes the actions of nicotine, barium and potassium (57).

4. Other ganglionic blocking actions

In the experiments showing that α-β-Ethylal-γ-trimethyl-ammonium-propanediol (2268F) possesses ganglion stimulating action, hexamethonium has been used successfully to inhibit this stimulant effect on the superior cervical ganglion (1). Hexamethonium will abolish the pupillodilator action of cervical sympathetic stimulation. This action is considerably more sensitive to block by hexamethonium than is contraction of the nictitating membrane (121), as it is to botulinum toxin (3).

The hypoglycaemic effect of insulin in dogs (153) and rabbits (105) is potentiated by hexamethonium, so far that a given dose of insulin, previously subconvulsive, sometimes becomes convulsant. The effects of hexamethonium in the unanaesthetized dog (tachycardia, ptosis, relaxation and injection of the nictitating membrane, dryness of the nose and shivering) have been compared to those of sympathectomy.

5. Other actions of hexamethonium of uncertain mechanism

The ganglion-blocking action of hexamethonium accounts for almost all the effects it produces in animals and man, and its specificity lends interest to three other actions less easily interpreted:

(1) Antagonism to certain carotid body stimulants. It has been shown that acetylcholine, nicotine and lobeline no longer elicit deepening and acceleration of respiration if hexamethonium is applied to the carotid body. Even with enormous doses of hexamethonium, however, the stimuli of asphyxia or cyanide remain effective (47). There is some discussion as to whether there is an afferent ganglionic synapse on the pathway of the carotid chemo-receptor mechanism, and it is possible that hexamethonium paralyses this. If there is not, then hexamethonium must be regarded as antagonising the action of the cholinergic drugs at a neuronal site other than the ganglion cell.

(2) Antagonism to the stimulant effects of acetylcholine-like drugs on the skin. A parallel situation exists in the skin (48). Although hexamethonium has no local anaesthetic action and gives rise to no disorders of sensation in man, it will prevent the afferent discharge aroused by an injection of acetylcholine or nicotine into an isolated skin preparation. There is no question of a peripheral synapse here, so that hexamethonium must be antagonising acetylcholine-like effects exerted on a peripheral axone.

These two observations give rise to a qualification of the specificity of hexamethonium. Its most obvious action is to prevent the excitation of the ganglion cell by acetylcholine released at the preganglionic nerve endings. But since it

prevents excitation of other nervous tissue by artificially applied acetylcholine-like drugs, it may be that its action is not restricted to the ganglion, but is fundamentally to prevent such excitation of nervous structures wherever it can be achieved.

(3) Of interest, therefore, is the third action of hexamethonium, that of central nervous depression. Large doses certainly depress the respiration, particularly in the barbitalized animal, without any neuromuscular block of a degree adequate to account for this (38, 142). It leads to a diminished anaesthetic requirement in man, and causes sleepiness in some subjects (179, 121). Finally, it abolishes nicotine convulsions, but not the tremor induced by nicotine (24, 34, 104). No doubt these actions could be attributed, in whole or in part, to block at a cholinergic synapse in the central nervous system. It will, however, require careful analysis to verify that peripheral block of ganglia cannot indirectly produce such effects, before this speculation can be accepted.

6. Factors influencing the response to hexamethonium

Although under standardized conditions hexamethonium has a highly reproducible action, the intensity of its effects may readily vary from one preparation or patient to another according to the conditions.

(a) *Background tone.* If the action studied is the reduction of some spontaneous autonomic function, such as that of the normal vasomotor tone, then hexamethonium will necessarily do no more than remove the background of ganglionic activity concerned. Hence the same dose may give a large fall in blood pressure in a recently anaesthetized cat with high vascular tone, a much smaller one in the same animal after lapse of time, and none at all in the pithed animal. Likewise the effect on the pupil, the heart rate of the alimentary motility depends on the autonomic activity to which the organs concerned are subjected.

(b) *Variations in sensitivity.* Ganglia are not all equally sensitive to blocking agents, and differences occur not only between different ganglia (79) but even, as Langley showed long ago, between different cell groups within a ganglion. With hexamethonium, it is much easier to paralyse the secretion of the salivary gland to chorda stimulation than the contraction of the nictitating membrane to cervical sympathetic excitation (132a) and the latter is also resistant compared to the dilatation of the pupil elicited (121); it needs, indeed, very large doses of hexamethonium to abolish completely the response of the nictitating membrane to brief tetani. Not only do different ganglia respond in different degree to a single drug, but the pattern of responses differs when the drug is changed. Some emphasis was placed on this in the early work, and it appeared possible that the relatively intense effect of pentamethonium on the superior cervical ganglion compared to that on the peristaltic reflex of intestine, in contrast to the intense relative effect of hexamethonium and tetramethonium, reflected a differing relative action on the sympathetic and parasympathetic components of the autonomic system (142). This simple picture has failed to survive, particularly because all agents paralyse salivary secretion first (132a). But it is clear that ganglia do in fact differ, so that the possibility remains open of devising blocking agents directed in their effects to one particular set of ganglia.

(c) *The possibility of maximal block.* It is not always possible to obtain complete abolition of ganglionic transmission, even with large doses. In particular the blood pressure level after hexamethonium never falls to that of a pithed cat; and the difficulty of complete paralysis of the nictitating membrane to a brief tetanus has already been mentioned.

(d) *Intensity and duration of activity.* The effect of hexamethonium on a ganglion depends on the activity of the ganglion, both at the time of administration and previously. Thus a freshly established tetanus may be well-maintained for a brief period, and then wanes considerably. Again it may be shown that as excitation is prolonged, the sensitivity of the ganglion increases. Similarly, the higher the rate of stimulation, the smaller the dose of hexamethonium required to produce a given reduction in transmission.

This relationship between activity and transmission block is very similar to that which exists in the curarized muscle, and in both instances it may be that a dwindling of the acetylcholine output with continued or accelerated frequency of nerve stimulation enables hexamethonium or curare to exert its blocking action more readily.

(e) *Compensatory mechanisms.* The tolerance to the hypotensive actions of hexamethonium which develops in hypertensive patients on regular dosage suggests that the effects of the drug may be distorted by compensatory mechanisms of one sort or another. Reactions of this kind, of course, take place whenever the blood pressure is changed, and hexamethonium, in fact, helps to reveal their occurrence, *e.g.*, the abbreviation and curtailment of the effects of adrenaline by buffer nerve reflexes.

Some care is needed, therefore, in interpreting the precise significance of a given depression of ganglionic activity, and comparisons can only be satisfactorily made at present when the ganglion used, the rate of preganglionic excitation, the duration of activity and the compensatory mechanisms are standardized.

7. Hypertension

The increasing recognition that nervous factors play an important part in hypertension has led first to the use of surgical sympathectomy in its treatment and later to the use of drugs which weaken vasoconstrictor tone. Among such drugs, those which paralyse autonomic ganglia offer certain advantages, particularly that the blood vessels are not themselves affected. In the event of overdosage producing too great a hypotension, sympathomimetics can therefore be used as antidotes; this is of course difficult if the hypotension is produced by substances antagonizing the effects of adrenergic nerves or of sympathomimetic amines. Tetraethylammonium was the first ganglion blocking drug to be used, and although its transient action and side effects limited its success, experience with it made it obvious that treatment on these lines was worth investigating. Hexamethonium has proved much more suitable, by reason of its more prolonged and purer action, and extensive clinical trials have been conducted (5, 6, 11, 17, 32, 35–37, 58, 61, 64, 65, 75, 102, 107, 109, 116, 122, 146, 150a 152a, 159, 160–162, 168–170, 177).

The fall in blood pressure produced in hypertensives by hexamethonium is largely due to the removal of abnormal sympathetic constrictor tone and it can be roughly matched by the fall obtained if the central nervous autonomic drive is reduced by sedatives. The effect obtained varies considerably, corresponding no doubt to the relative proportions of the neurogenic and humoral components of the raised blood pressure (*cf.* 6 and 62, 63). In almost every case, however, a reduction in the blood pressure can be obtained if the patient is in the erect posture, because of the depression by hexamethonium of postural vaso motor reflexes. This postural hypotension is an essential element in the use of hexamethonium and is not to be regarded as a side effect.

From the clinical reports already published, particularly those by Campbell and Robertson, Smirk and his colleagues, Turner, Rosenheim, and Finnerty and Freis, there is no doubt that hexamethonium properly used in the right patients can produce considerable symptomatic and objective improvement in cases of hypertension. Patients with the more severe and complicated forms of the disease are those that benefit most. Headache, breathlessness and dizziness are almost invariably improved. Papilloedema and retinal damage usually regress. Cerebral oedema and vomiting can be relieved. Pulmonary oedema may be lessened or resolved (61) and cardiac hypertrophy diminished. In the few cases of toxaemia of pregnancy and eclampsia whose treatment has been described, hexamethonium has proved successful in permitting a live birth or in terminating *status eclampticus* (144, 168). The action of hexamethonium is enhanced by a salt-poor diet.

In milder cases of hypertension with a good prognosis, a full clinical assessment of the advantages to be gained has yet to be made. There are certain difficulties in successful treatment against which therapeutic gain has to be balanced. In the first place oral administration has not proved satisfactory as was at first hoped because of the poorness and irregularity of absorption. Consequently parenteral routes must be used in most (but not all) patients (73, 150a) and an "insulin regime" of subcutaneous or intramuscular injections, developed by Smirk and his colleagues, has proved to be the most generally effective means of treatment so far. Secondly, the dose required by a particular patient is difficult to predict, since the effect depends on a large number of variables discussed below. This means that treatment of a patient requires careful individual adjustment, best initiated in the hospital, and that it needs continuous supervision thereafter. Thirdly, since the action of hexamethonium is due to competitive block of the ganglionic synapse, partial block of ganglia other than those controlling the blood pressure may lead to actions commonly but loosely termed "side effects." The most important of these are due to paralysis of parasympathetic ganglia, *i.e.*, constipation, rarely leading (especially after big oral doses) to ileus (20, 108, 111, 115, 167), difficulty in micturition, and interference with pupillary and ciliary reactions to light and accommodation. Constipation usually responds to liquid paraffin or purgatives and ileus (if allowed to occur) has been successfully treated by neostigmine (20). Pilocarpine (150a) and carbachol (65) have also been used to overcome the effects of parasympathetic blockade. Sometimes the postural hypotension from depression of

sympathetic vasomotor reflexes may be so severe as to cause faintness or collapse (10), particularly when the blood pressure is greatly reduced too abruptly. The hypotension responds to sympathomimetic amines, as expected from the mode of action of hexamethonium (14), but infusions of adrenaline have proved dangerous. The use of posterior pituitary extract has been suggested (29). Grob and Harvey (75), after showing that neostigmine failed to diminish this hypotensive effect, drew the conclusion that "the blocking action of hexamethonium does not appear to be the result of competitive inhibition of acetylcholine." All the weight of the evidence, already discussed, is against this suggestion, and their results may well follow from the fact that antiesterases reveal their rather weak action at the ganglionic synapse only under special experimental conditions. Bromism occurred in some patients when hexamethonium bromide was adminstered, particularly when this treatment was combined with a low sodium diet (89, 107, 150, 163), but this can be avoided by using other salts.

In addition to the therapeutic results of the use of hexamethonium, certain facts have emerged of some general physiological and pathological interest. The first of these is that during the first few weeks of repeated administration the hypotensive effects of hexamethonium usually wane and the dose required to produce the original depressor effect increases, although after this period a regular maintenance dose can be achieved. This "tolerance" is lost again when hexamethonium is withdrawn. Tolerance does not appear to be due to any increased rate of excretion of hexamethonium or to the development of a "detoxicating" mechanism (121). Its significance is obscure, but it may be compared either to the recovery of vascular tone after sympathectomy or to a compensatory development of humoral vasoconstrictor activity. It must be remembered, however, that tolerance develops to the effects of most drugs when these are given over a prolonged period.

A further important finding, already briefly mentioned, is the variability of the response of human beings to the drug. At least four factors may contribute to this: 1) differences in the postural reaction, depending probably on the vigour of the reflexes, on the peripheral blood flow and on the muscle tone of the individual; 2) differences in the intensity of sympathetic tone; 3) differences in absorption of hexamethonium from the intestine or even (to some extent) from its subcutaneous or intramuscular injection site; 4) differences in its distribution throughout the body and in the renal blood-flow on which its excretion depends. Quite widely divergent curves of concentration of hexamethonium in the plasma against time may be obtained, even with normal subjects (121).

The variability of response in man thus reflects not so much an irregularity in the action of hexamethonium on ganglia but the differences in sympathetic tone, in reflex function, and in absorption, distribution and excretion of the drug. It must be expected to occur with any drug with the same mode of action.

8. Reduction of bleeding during surgical operations

An important innovation is the use of ganglion-blocking agents for reducing bleeding at surgical operation (45, 54, 55, 56, 91, 106, 158). It had been earlier shown that lowering the blood pressure by spinal anaesthesia, or by temporary

withdrawal of blood diminished considerably the bleeding during plastic operations and ear, nose and throat surgery. Hexamethonium has proved to be equally or more effective for this purpose, and considerably easier to handle. The desired reduction (to c. 60–70 mm. mercury) cannot be produced by hexamethonium alone in a supine patient, and postural assistance is usually employed. After sympathetic tone is reduced or abolished by hexamethonium, blood can be pooled in the vessels of a dependent part of the body (usually the legs or viscera), thus lessening the cardiac output (177) and hence bringing the blood pressure down to the desired level. Suction applied to the legs has also been used for this purpose (152). In addition, the operative field can be further exsanguinated by raising that part of the body in which it lies above the rest, so that the blood is drained away from it. When the operation is over and the effect of the drug passes off, there appears to be no increased liability to reactionary haemorrhage. Presumably clotting takes place in the relaxed vessels just as in vessels with normal tone, and with recovery of tone and contraction of the vessel the clot might even become more firmly held.

This technique has been particularly successful in plastic surgery, ear, nose and throat surgery, in thyroidectomy and in mastectomy, and it may greatly facilitate and abbreviate operation. Satisfactory results have also been reported in thoracic, abdominal and pelvic operations.

The doubt naturally occurs whether the blood supply to the brain, heart and kidneys remains adequate during such hypotension. It has been shown that the renal circulation at least is not greatly reduced, although anaesthesia itself may lower it considerably (119). This result implies that compensatory vasodilatation in the kidney occurs. Considerable attention has been paid by anaesthetists to the state of the heart, particularly in older patients subjected to this technique, but no electrocardiographic signs of coronary ischemia could be found in either young or old patients with pressure reduced to 60–70 mm. mercury (55). Hexamethonium has proved of great assistance to the neurosurgeon, diminishing haemorrhage and improving the visibility (particularly with vascular tumours), lessening intradural pressure and cerebral oedema and greatly accelerating the operation. Given careful control of posture, no cerebral damage occurs and normal encephalograms have been obtained throughout such operations (78, 176). Attention has been drawn to the danger of anoxic liver damage, with release of V. D. M., if the blood pressure falls below 60 mm. (26).

Apart from the premeditated reduction of haemorrhage during the whole of an operation, hexamethonium has been employed to control unexpected haemorrhage; thus bleeding from a pulmonary vein and from a gastric artery were successfully and rapidly checked (80, 148).

The hypotensive technique has proved remarkably promising and has posed many interesting physiological problems (127). The fact that so low a pressure can be sustained for a period of hours with little deleterious effect is remarkable, and provides a complete contrast to the effects of similar hypotension due to haemorrhage. The difference is no doubt due to the fact that, whereas with hexamethonium capillary blood flow may well be normal or even increased, after

haemorrhage it will certainly be reduced. But until more work has been done in this field, it is difficult to be certain of all the factors involved in the reduction of blood pressure and of haemorrhage, and of their relative importance. For instance the hypotheses that relaxation of venous tone contributes to the postural effects, that the capillary pressure does not fall as the blood pressure falls and that the raised operative field is more or less ischaemic, have not been directly established.

Although hexamethonium given before operation diminishes or prevents haemorrhage, it may, when given after a haemorrhage, accentuate considerably the fall in blood pressure resulting from the loss of blood (55, 66). If this occurs, however, the blood pressure can be promptly restored by blood transfusion. Similarly in the cat, small doses of hexamethonium greatly increase the depressor effect of haemorrhage (129). Such experiments bring into great prominence the role of nervous factors in maintaining a stable blood pressure in the face of alterations of blood volume. For practical purposes, it is essential to grasp that, after hexamethonium, the patient's circulatory needs have to be cared for by the anaesthetist just as after a muscle relaxant artificial respiration must be available, and that in both situations the normal neural control is suspended. Given an understanding of this point, however, there seems to be no reason why "controlled circulation" should not be as safe as "controlled respiration."

9. Actions on the human alimentary tract

Investigations into the action of hexamethonium on gastric function were initiated by Kay and Smith (97) who showed that hexamethonium given intramuscularly to fasting patients could depress the volume and acidity of the gastric secretion occurring spontaneously or in response to insulin, to the point of achlorhydria. Gastric secretion elicited by histamine, alcohol or meat extract was not affected. Depression both of the volume and pepsin content of the nocturnal "interdigestive" secretion occurs, and the reduction is of the same magnitude or greater with hexamethonium as with *l*-hyoscyamine or with vagotomy (151). Later experiments showed that similar effects could be obtained by oral administration of hexamethonium, although less consistently than with parenteral administration. Gastric motility is also inhibited, sometimes completely, and for many hours (98, 99). Slowing of the emptying of the stomach and small intestine has been demonstrated by X-ray after barium meals. The effects both on secretion and on motility are less pronounced when the stomach is full (51). Clinically, hexamethonium often relieves the pain of peptic ulcer, and a careful preliminary trial suggests that its actions in depressing secretion and motility may actually accelerate healing (155). Full assessment of its usefulness must, however, wait for a clinical trial prolonged enough to allow control of the well-known spontaneous remissions in the disease.

10. Comparison of tetra-, penta- and hexamethonium

In the original pharmacological studies, attention was drawn to the apparent difference in relative activity of the various ganglion-blocking salts on sym-

pathetic and on parasympathetic ganglia. It was hoped that such differences might be exploited clinically where the ganglia concerned differ (*e.g.*, hypertension and peptic ulcer), so that for instance hypotension could be avoided in the treatment of peptic ulcers, or intestinal effects avoided in the treatment of hypertension. Tetra-, hexa- and pentamethonium furnished a series with increasing effect on the sympathetic superior cervical ganglion of the cat relative to the action on the parasympathetic peristaltic reflex, such that if hexamethonium were regarded as equally active in both tests, then pentamethonium is 2½ times more active on the superior cervical ganglion than on the peristaltic reflex, and tetramethonium is 3 times less active. In practice, however, these differences have not proved large enough to be clinically useful, and no evidence has been obtained in man that tetramethonium and pentamethonium differ qualitatively from hexamethonium (17, 54, 93, 99). The only difference between these three drugs in man is that pentamethonium is somewhat less active, and tetramethonium much less active than hexamethonium.

11. Other actions of hexamethonium in man

The most valuable effects of hexamethonium therapeutically are the reduction of blood pressure, the diminution of haemorrhage at operation, and the depression of gastric secretion and motility. But many other less important actions have been described. Depression of sympathetic vasomotor tone leads not only to postural hypotension, but also to an increase in limb blood flow (especially of the leg and foot) accompanied by a rise in skin temperature, to a depression of the reflex pressor responses accompanying application of cold to the hand or following the Valsalva manoeuvre, and to a sensitization to the effects of venous congestion of the limbs, or of changes of hydrostatic pressure in an immersed subject (66, 147). These reflex responses, particularly the postural vascular reflexes, seem to be particularly sensitive to hexamethonium, and in normal subjects at least postural hypotension persists long after the blood pressure measured in the supine position has returned to normal.

Hexamethonium causes a dilatation of the pupil, lessens the reaction of the pupil to light and to accommodation, and weakens the accommodation of the lens. In addition there is usually a slight injection of the conjunctiva, and dryness of the eyes. The mouth, throat and larynx are also sometimes noticed to be drier than usual after hexamethonium, and sweating may be considerably decreased (32, 121).

Pentamethonium and hexamethonium have been used in a few cases of peripheral vascular disease (5, 32, 59, 154), but equally or more effective means which do not involve a general ganglionic action are usually available. Hexamethonium has been successfully used in causalgia (149), exerting its action probably by relieving sympathetic vasospasm of the vessels supplying the injured nerve or adjacent regions. A curious observation is that hexamethonium may relieve hiccup (84, 113). It has also been shown to antagonise the stimulating action of lobeline on the carotid body (85).

12. Toxicity

In the original studies, when large daily doses of hexamethonium were given intravenously for a month to rabbits, no toxic effects were found. This absence of toxicity has been confirmed in human experience. Despite the large quantities of the drug which must by now have been administered to many patients, for periods of sometimes more than 2 years, no case has yet been described recording damage of the haematopoietic system, liver, kidney or other organs, or sensitization phenomena of any sort. This freedom from toxicity is no doubt attributable in part to its extracellular existence and in part to its physical and chemical inactivity and stability, factors all closely related to its quaternary character.

VII. Other Members of the Methonium Series, and Other Actions

With chain lengths shorter than C4, the series becomes very inactive, and C2 and C3 are surprisingly inert pharmacologically, and are in all respects weaker than tetramethylammonium to which they bear so close a relation. At the other extreme, with chain lengths greater than 10 carbon atoms, activity again falls away, although less rapidly. An anticholinesterase action becomes fairly prominent, *in vitro* at least, although it is always small compared with eserine; its main interest is that for certain members (C12 in particular) the activity is greater against red blood cell esterase than against plasma esterase; most compounds inhibit the latter more readily. A very feeble muscarine-like action also appears, reaching a maximum at C12–C13. The longest chained member tested, C18, is surface-active, and to this is probably attributable a weak antibacterial action against *E. coli*, streptococci and staphylococci in concentrations of 0.3–8 parts per 100,000.

VIII. Specificity, Potency, Site of Action and Chemical Structure

From the theoretical point of view, it is interesting that such simple molecules as hexamethonium and decamethonium should be so specific in their actions. Most of the drugs used in pharmacology for their potency and specificity, being often of natural origin, have had a relatively complex structure (*e.g.*, physostigmine, *d*-tubocurarine, toxiferine I, atropine). This has led chemists to use such complex molecules as their models in preparing drugs of like action synthetically. Of recent years, however, a progressive simplification has taken place which can be seen, for instance, in the development of flaxedil from 8′,8″-diquinolyloxy-1,5-pentane di-iodethylate by Bovet, of neostigmine from eserine by Aeschlimann and Reinert and of sulphonamides from the prontosil dyes. The simplicity of structure of the methonium salts emphasizes this development, although obviously the limit of simplification has been reached in that particular direction. It is notable that with drugs acting at the neuromuscular junction their structure has become steadily nearer that of acetylcholine, just as the successors to the prontosil dyes became more and more like *p*-aminobenzoic acid. All this suggests that, in developing new substances with potent pharmacological actions, it is safer to use as models substances occurring naturally in the body rather than those more complicated alkaloids through which so much physiological

knowledge first came to light. It seems further that simplification of the molecule, so far from allowing side actions to multiply, in fact diminishes them; for both hexamethonium and decamethonium compare very favourably with natural alkaloids in their freedom from such actions. This process, of course, can only be taken up to a certain point; the simplest salts, tetraethylammonium and tetramethylammonium, representing completely unencumbered active quarternary radicals, lose the specificity of hexamethonium or decamethonium both as to site and type of action.

Despite the simplicity of these compounds it is still very difficult to relate their activity and specificity to their chemical structure. The literature is full of shipwrecks in the quicksands of 'structure-action-relationship,' and it is obvious that our biophysical knowledge is inadequate to the pharmacological strains placed on it. It is worth while, however, to mention briefly some of the points which a satisfactory theory would have to take into account even when we restrict the problem to the neuromuscular and ganglionic synapse.

Acetylcholine, at the endplate or in the ganglion, reacts not only with the specific receptor surface but also with cholinesterase. A drug resembling acetylcholine can thus reveal its likeness in three ways: by mimicking acetylcholine; by competitively antagonizing it; and by antagonizing the activity of the cholinesterase. We may have, therefore, among the effects of such a drug, excitation or competition at the endplate or in the ganglion, as well as antiesterase activity, quite apart from any peripheral autonomic 'muscarinic' actions of central actions. The theory, therefore, must account for the way in which a drug such as decamethonium or hexamethonium can select, from the protean manifestations of acetylcholine action, that of endplate stimulation or of ganglion competition alone.

The structural factors determining the site of action, the mode of action, and the potency of hexamethonium and decamethonium can be brought out by comparing them with each other and with compounds closely related to them chemically; even with such elementary structures, four factors can be distinguished:—

(a) *Interquaternary distance.* Comparison of hexamethonium with decamethonium shows that the interquaternary distance determines both their site and mode of action, and it is extraordinary that a change which looks so simple in terms of chemical structure should transform so fundamentally the pharmacological action. Even the slighter change from hexamethonium to tetramethonium or from decamethonium to octamethonium produces great reductions in potency. The peaks of activity at C5–C6 and C10 have prompted a good deal of speculation and synthetic chemistry. Among the other series prepared possessing neuromuscular or ganglionic activity, some have a peak of activity corresponding to one of those in the methonium series, but this is by no means the rule. Similar maxima exist among chemotherapeutic agents and in the histamine-liberating aliphatic diamines. Unfortunately there is no certain knowledge as to the actual interquaternary distance in compounds with flexible chains of this sort. There is, therefore, a good deal of doubt as to the interpretation of the

significance of the chain-lengths of hexamethonium and decamethonium, and the idea that the length of the chain necessarily corresponds to an interreceptor distance has been questioned (110). Another suggestion is that it corresponds rather to a certain molecular bulk just capable of occluding a certain critical receptor area. Nevertheless, the lengths concerned are so sensitive to alteration that considerable importance attaches to them, and the naive view that they represent some measure of interreceptor distance need not be abandoned.

(b) *Interquaternary structure.* The structural differences between decamethonium and succinylcholine do not lead to very noticeable differences of action apart from the susceptibility of the latter to hydrolysis. But the inclusion of aromatic nuclei between the basic groups has a more radical effect, usually in rendering the drug more competitive in nature and often less specific.

(c) *The central atom of the terminal groups.* It has been shown since the work of Ing and Wright that substitution of nitrogen by sulphur, phosphorus or arsenic leads to a similar but progressively weaker activity. Similarly with the bisonium salts, the bis-sulphonium compounds are distinctly feebler than the corresponding bis-ammonium compounds (176a). There is no rival so far to quaternary nitrogen for biological potency among onium salts.

(d) *The groups substituted on the basic nitrogen.* If the methyl groups in decamethonium are all replaced by ethyl groups the compound is much less active, and becomes a competitive blocking agent as well as acquiring appreciable action in paralyzing ganglionic transmission. A similar transition is known for adipylcholine, which loses its power of producing acetylcholine-like effects at the neuromuscular junction as soon as more than one methyl group is replaced by ethyl (71). The situation seems to be comparable with the result of changes in the molecule of acetylcholine itself; Holton and Ing (90) showed that, although a single substitution of an N-methyl group by an ethyl radical had only a small effect on the activity of the molecule, any further substitution changed it radically.

Even when all these structural considerations are taken into account, however, it is still impossible to state the expected action of a compound. This is particularly obvious with decamethonium, whose expected action cannot be predicted unless the species and even the muscle on which it is tested is known. In other words, the receptor structure too must always be considered, and cannot be assumed to represent a constant framework from animal to animal into which chemical structures of varying ingenuity may be fitted.

IX. Conclusions

The detailed pharmacological analysis of hexamethonium and decamethonium has elucidated fairly completely their site and mode of action. Once this was done, and their remarkable specificity appreciated, they became at once useful research tools in the hands of pharmacologists and physiologists. First one may quote the clear distinction that can be made between the two types of neuromuscular block, each now easily recognized by its own characteristic syndrome of responses. Blocks distinguishable in the same way by deficiency or excess of

the excitatory process can be recognized also at the ganglionic synapse. No doubt, in due course, other substances will appear as specific for the central nervous synapse as the methonium salts have been for the neuromuscular junction and ganglionic synapse, and our new knowledge about the peripheral synapses should help greatly in disentangling what is at present a very difficult picture.

Another valuable development has been the addition to our knowledge of the pharmacology of the human organism, which has lagged far behind that of animals. The similarity of human muscle to the muscle of the cat, the different reactions of 'red' and 'white' muscle, the resistance of the myasthenic to decamethonium, the effects of hexamethonium in man and particularly the fact that the blood pressure may be safely reduced by it to levels commonly regarded as exceedingly dangerous,—all these represent stimulating observations from which fruitful developments may be expected. It is beyond the scope of this review to comment in general on the clinical usefulness of quaternary salts in the future. But whatever new discoveries are made, whether in extending the use of the methonium salts themselves or in developing new compounds with a more advantageous balance of actions, the specificity, potency, versatility and freedom from toxicity of the methonium compounds must provide a great encouragement and guide to research in this direction.

At the outset of this review some mention was made of the background to the study of compounds such as the methonium series. The growth of electrical recording methods, of synthetic chemistry, and of clinical trial and investigation have all played their part. But reflection on the fundamental ideas involved and the experimental techniques required show that among the developments leading to this therapeutic harvest, the bringing to fruition of the theory of chemical transmission at the neuromuscular and ganglionic synapses must occupy pride of place.

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